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Global trends and challenges in deceased donor kidney allocation

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Keywords

Deceased donor, kidney transplantation, kidney allocation, longevity matching, survival prediction, equity of access

Abstract

Worldwide, the number of patients able to benefit from kidney transplantation is greatly restricted by the severe shortage of deceased donor organs. Allocation of this scarce resource is increasingly challenging and complex. Striking an acceptable balance between efficient use (utility) and fair access (equity) to the limited supply of donated kidneys, raises controversial but important debates at ethical, medical and social levels.

There is no international consensus on the recipient and donor factors that should be considered in the kidney allocation process. There is a general trend towards a reduction in the influence of human leukocyte antigen mismatch and a rise in the importance of other factors shown to affect post-transplant outcome, such as cold ischaemia, duration of dialysis, donor and recipient age and comorbidity. Increased consideration of equity has led to improved access to transplantation for disadvantaged patient groups. There has been a welcomed overall improvement in the transparency and accountability of allocation policies. Novel and contentious approaches in kidney allocation include the use of survival prediction scores, as a criterion for access to the waiting list, as well as at the point of organ offering with matching of predicted graft and recipient survival.

This review compares the diverse international approaches to deceased donor kidney allocation and their evolution over the last decade.

Introduction

The superior outcomes of kidney transplantation over dialysis, and the growing incidence of end-stage renal disease (ESRD), have led to an exponential rise in the need for kidney transplantation worldwide.¹ In contrast, the number of deceased donors has changed little and is vastly insufficient.² Consequently, patients face longer waiting times, as well as a higher risk of morbidity and mortality while on the waiting list. In the US alone, the number of patients on the waiting list has doubled over the past decade reaching around 100 000 patients, median waiting time has increased by 50% to over 4.5 years and nearly 5000 patients die whilst waiting for a deceased donor kidney transplant every year.³ Similar trends have been noted in other countries (Figure 1 and Table 1).

While living donors usually donate to a specified recipient, in most countries deceased organ donation is non-directed and organs are offered to patients on a waiting list via an allocation scheme. Allocation schemes are generally governed by appointed transplant organisations that may operate at a regional, national or even international level. Ownership of deceased donor organs is a controversial matter; in some countries they are considered a national resource, while in others they are retained within the donor region, and sharing between regions may be limited to payback requirements. Thus allocation schemes vary from simple local programmes to complex national algorithms. Furthermore, there is no universal consensus on the factors that should be considered in the allocation process, leading to considerable variation in the way patients are prioritised within different schemes.

The major debate in the allocation of scarce donor organs centres on the competing ethical values of utility (maximum outcomes) and equity (fairness). Consideration must be given to the efficient use of organs to optimise outcomes and the overall benefit to society, but also to

the welfare of individual patients and fair access to transplantation.⁴ Utility-based allocation prioritises patients with the best chance of a favourable outcome, aiming to achieve the maximum benefit from every transplanted organ. Inevitably, this gives rise to debate over how benefit should be measured – i.e. graft survival, patient survival, life years gained from transplant or quality of life? Furthermore, it disadvantages patients less likely to experience a good outcome, such as patients who are older, diabetic, have more comorbidity or have been on dialysis for a longer period of time.⁵⁻⁹ An increasing proportion of patients on the waiting list fall into these categories, yet still derive a significant survival benefit from transplantation.^{1, 10-12} The principle of equity necessitates fairness in organ allocation, however this may be interpreted in various ways. Equity is commonly conceived as “equal opportunity” i.e. every person who may benefit from a transplant should have equal opportunity of receiving one.¹³ It is important not to misinterpret this as equality; although equality involves treating all patients exactly the same (i.e. allocation by lottery), it neglects the fact that patients do not start from equal circumstances.¹⁴ The discovery of HLA-matching as a major determinant of graft survival led to its principal role in the first formal allocation schemes.¹⁵⁻¹⁷ However, it became apparent that such schemes resulted in inequitable access to transplantation for difficult to match patients.¹⁸⁻²⁰ Consequently, most schemes now award extra priority to highly-sensitised patients and patients with rare HLA-types (most commonly from ethnic minorities) who are biologically disadvantaged in finding a compatible donor, in order to equalise their opportunity for transplantation. “Queuing” (first-come, first-served) is another concept of equity that has been widely accepted in kidney allocation. However, with the increasing age and morbidity of patients on the waiting list, this approach has been challenged for favouring those who are able to survive the ever-increasing wait. Furthermore, with growing evidence for disparities in access to the waiting list, many schemes now measure waiting time from the start date of dialysis as opposed to the listing

date, although some countries are yet to adopt this approach. Priority for paediatric patients is universally acknowledged in view of the detrimental impact of renal failure and prolonged dialysis on growth and development (although the age cut-off and level of priority varies substantially between different schemes). In contrast, the prioritisation of younger adults over older adults is widely disputed. While advocates of the “fair innings” concept believe equity should be measured by the opportunity to reach a normal life expectancy, critics argue that preferential allocation to younger patients is age discrimination.²¹ The “prudential lifespan” provides an alternative concept of equity through the allocation of kidneys by age-matching. This justifies the allocation of younger (and therefore “higher quality” kidneys) to younger recipients and the allocation of older kidneys to older recipients since all patients are treated similarly in a particular stage of life.²² However, this approach becomes problematic if there is a discrepancy in the age distribution of donor and recipient pools. Moreover, age is just one of many factors which influence the outcome of transplanted kidneys. A range of survival predictors are utilised in the emerging concept of longevity-matching, where kidneys are allocated based on matching of estimated graft and recipient survival. This approach remains controversial, reflecting the enduring difficulties in achieving an acceptable balance between utility and equity.

This review compares the allocation schemes of several different countries and explores their evolution over the last decade.

United Kingdom

The first UK national kidney allocation scheme was a simple HLA-matching scheme introduced in 1989. One kidney from each donor was allocated nationally to a “beneficially

mismatched recipient” (defined as HLA-A, -B and -DR mismatch 000, 100 or 010), while the paired donor kidney was allocated locally according to individual centre policies.^{17, 23}

A revised scheme was implemented in 1998, after three distinct tiers of HLA-mismatch were identified as major influences on graft outcome.²⁴ Allocation was prioritised to tier 1 (000 mismatch) followed by tier 2 (100, 010, 110 mismatch) patients nationally, otherwise allocation was on a local basis to tier 3 patients (all other HLA-mismatch grades). Within tiers 1 and 2, priority was given to paediatric patients (<18 years), patients disadvantaged in finding a compatible donor (highly-sensitised [panel reactive antibody, PRA ≥ 85%], HLA-DR homozygous and blood group B) and local patients. A points score differentiated equally eligible patients within the tiers, based on recipient age, donor-recipient age difference, waiting time (from listing date), matchability score, level of sensitisation and balance of organ exchange between centres. Matchability was a measure of the likelihood of being offered a well-matched kidney (tier 1 or 2); the aim being to improve access for difficult to match patients. However, because the points score was employed only to differentiate equally HLA-matched patients, the overall effect of the point-scoring factors proved to be minimal. Although the 1998 scheme improved the level of HLA-matching of allocated kidneys, inequity of access remained a significant issue.²⁴

In 2006 a new scheme was implemented and this remains in place to date, albeit with minor modifications.²⁵ Previously deemed non-favourable levels of HLA-mismatch were shown to be achieving good outcomes, therefore the new scheme places less emphasis on HLA-matching and except for zero HLA-matches, HLA-A matching is no longer taken into account.⁸ Zero HLA-mismatched patients retain top priority along with well-matched (100, 010, 110) paediatric patients, HLA-DR homozygous patients and highly-sensitised patients

(now measured as calculated reaction frequency, cRF, 85%). cRF is the percentage of 10 000 recent donors that the patient has pre-formed antibodies against. The points score was also revised; where previously waiting time contributed the least points, it now has potentially the greatest influence (although continues to be defined as time from listing). Points for recipient age are combined with HLA-mismatch in a novel approach to prioritise younger patients for well-matched grafts. This minimises HLA-sensitisation and improves the likelihood of re-transplantation, which is particularly crucial for younger recipients who are likely to require more than one graft in their lifetime. Other point-scoring factors include the proximity of the donor to the recipient centre (to minimise ischaemia), donor-recipient age difference, HLA-DR and –B homozygosity and blood group (to address imbalances of distribution between donor and recipient pools). Since the matchability score proved to be unsuccessful in improving equity, the 2006 scheme utilises a different approach whereby rare HLA-types are defaulted to more common related HLA-types against which cross-reacting antibodies seldom form. In September 2014, the national scheme was extended to include allocation of donors after circulatory death (DCD). In the phase-in period this only applies to one kidney from DCD donors aged 5 to 50 years.²⁶

The 2006 scheme has successfully increased the number of transplants for highly-sensitised, long waiting, difficult to match and Black, Asian and minority ethnic patients, without compromising graft or patient survival (Table 2). Nevertheless, the past decade has also seen an overall increase in the size of the waiting list, median waiting time (Table 1) and the number of discarded kidneys.²⁷ This raises concerns over the efficiency and suitability of the allocation system within the context of an older and higher risk population of donors and recipients.

United States

The first US kidney allocation scheme was introduced in 1987, and a completely revised scheme was implemented for the first time in 2014.²⁸ Under the former system, the country was divided into 58 donor service areas (DSAs), responsible for local procurement and allocation of deceased donor organs.²⁹ Although there was mandatory national sharing of zero HLA-mismatched kidneys, these were required to be paid back to the procuring DSA. The large majority of organs were retained within and allocated by individual DSAs. Given that local organ supply relative to demand varied widely between DSAs, this led to substantial disparities in waiting time across the country.³⁰ In March 2000, the Department of Health and Human Services issued “The Final Rule” in order to establish a national framework for organ allocation and reduce geographical inequities.³¹ Following this, all kidneys were allocated via one of four sequences according to the category of the donor:

- Standard criteria donors (SCD) < 35 years
- SCD ≥ 35 years
- Expanded criteria donors (ECD)
- Donors after circulatory death (DCD)

ECD kidneys were defined by an estimated risk of graft failure 70% higher than SCD kidneys and were offered to specifically consented recipients.³² Within each sequence, priority was given to zero HLA-mismatched patients, blood group identical patients, highly-sensitised patients (cPRA ≥ 80%), paediatric patients (<18 years), prior live organ donors, local patients and DSAs owed a payback. A points score was used to rank individual patients (ECD/DCD recipients were ranked by waiting time only).³³ The points score was extensively modified over time towards fewer points for HLA-matching (except for zero HLA-mismatches, HLA-A matching was eliminated in 1995 and HLA-B matching eliminated in

2003) and more points for waiting time, reflecting efforts to achieve a more equitable system.^{34, 35} The “Share 35” scheme was implemented in 2005, which awarded extra priority to paediatric recipients for donors under 35 years and zero HLA-mismatched donors of all ages, but was unexpectedly associated with a decline in paediatric living donor transplants.³⁶

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Despite repeated efforts to improve the former system, it was perceived as inefficient and inequitable. Over the last decade, waiting list numbers doubled, death on the waiting list increased (Table 1) and average post-transplant survival deteriorated.³⁸ By 2011, 39 of the 58 DSAs were operating at least one variance to the national system, resulting in inconsistent allocation across the country.³⁹ Waiting time had become the dominant factor of allocation due to efforts to improve equity, but this created a system that was essentially a queue, with minimal regard for outcomes. As such, kidneys with a long predicted life-span were often allocated to patients with significantly shorter life expectancy, leading to high rates of death with a functioning graft and unrealised graft benefit. Similarly, younger patients were frequently allocated kidneys with a much shorter life span, resulting in high discard rates, re-transplantation rates and HLA-sensitisation.⁴⁰

The key concept of the new system is longevity matching, whereby the 20% of listed patients with the longest estimated post-transplant survival are prioritised for the 20% of kidneys with the longest estimated graft survival.²⁸ The Estimated Post-Transplant Survival score (EPTS) predicts patient survival based on age, time on dialysis, diabetes status and prior transplantation. Graft survival is estimated by the Kidney Donor Profile Index (KDPI); a continuous measure based on 10 donor characteristics (Table 3). This replaces the previous dichotomous ECD/SCD stratification of donor kidneys which inadequately reflected the risk

of graft failure.⁴¹ As before, kidneys are allocated through 4 sequences, now defined by the KDPI score of the donor kidney (KDPI $\leq 20\%$, $20\% < \text{KDPI} \leq 35\%$, $35\% < \text{KDPI} \leq 85\%$, KDPI $> 85\%$). Paediatric patients retain priority for zero HLA-mismatched kidneys and for KDPI $\leq 35\%$ kidneys. Local priority is also retained, but paybacks and local variances no longer permitted. Changes to the points system include calculating waiting time from the start of dialysis instead of listing and using a sliding scale of points for sensitisation level.

It is expected that the new scheme will enhance utility by an additional 9000 life years annually and improve transplantation rates for highly-sensitised, ethnic minority and patients 18-49 years. However it is acknowledged that the scheme will likely decrease access to transplantation for patients > 50 years.³⁹

Australia

Previously low donation and transplantation rates in Australia have increased significantly since implementation of the national Organ and Tissue Authority in 2008.^{2, 42} Remarkably, Australia is now one of few countries where waiting list numbers and median waiting time have reduced over the past decade (Table 1). The decline may be linked to the introduction of national listing criteria that restrict access to the kidney transplant waiting list to patients with an estimated 5-year post-transplant survival of over 80%.⁴³ These criteria are relatively strict compared with current European guidelines that recommend exclusion of patients with a life expectancy of less than 2 years.⁴⁴

The national allocation system was introduced in 2008. Only well-matched grafts are allocated nationally (maximum 2 HLA-mismatches at HLA-A, -B, or -DR if PRA $> 80\%$ and

at HLA-A or -B only if PRA<80%). Around 20% of kidneys achieve this level of matching whilst the remaining 80% are allocated locally via state-based algorithms. The national algorithm is based on a points system starting with a base score from which points are deducted or gained. Priority is given to zero HLA-mismatches, sensitised patients at 2 levels (PRA >50% and >80%), paediatric patients (<18 years), waiting time (from start of dialysis) and local patients. Balance of exchange is also taken into account. Although state-based algorithms differ, all are required to allocate a minimum of 30% of kidneys on waiting time alone, in order to improve equity for difficult to match patients.⁴³

New Zealand

New Zealand's organ donation and transplantation rates have remained inferior to those of other western countries (Table 1). New Zealand has a mainly white donor population, compared to an ESRD population consisting of a high proportion of Maori and Pacific Island Nation people, leading to inequity issues for difficult to match patients similar to the UK, US and Australia.⁴⁵

Access to the waiting list is determined by the same listing criteria used by Australia (estimated 5-year post-transplant survival of >80%) but in contrast estimates are calculated from a survival prediction tool, based on an index derived and validated in a US dataset of 170 000 patients.⁴⁶ Patients are rescored annually or at the time of any change in their health status, and removed from the waiting list if their score falls below 70%.⁴⁷

The structure of the allocation protocol is also similar to the Australian system, whereby patients start with a baseline score from which points are deducted for HLA-mismatches and gained for paediatric status (age <15 years) and waiting time (from start of dialysis).⁴⁸ Unlike

most other allocation systems, points are not awarded for HLA-sensitisation, as waiting time is considered a good enough surrogate for this. There are 2 levels of allocation; level 1 aims to allocate to well-matched patients (maximum of 2 HLA-A or -B mismatches) and level 2 to longer waiting patients.⁴⁹ The structure of the protocol has remained largely unchanged over the past decade with minor modifications implemented on the basis of audit data; HLA-DR mismatches were excluded from level 1 in 2013 to reduce the percentage of kidneys allocated in this level, age-matching was abolished as the majority of kidneys were from older donors and it became apparent that younger patients were being disadvantaged and waiting time was given increased weighting in the points score (personal communication, Ian Dittmer, 26/12/2014). A novel feature of the New Zealand kidney allocation scheme is that all ECD kidneys are biopsied, reviewed by an on-call pathologist and scored according to the Remuzzi classification. Kidneys scoring 4-6 are offered as dual transplants and those scoring 7 are discarded.⁴⁹

Eurotransplant

Eurotransplant was created in 1967 as an international collaboration between Austria, Germany, Belgium, Luxembourg and the Netherlands, and was later joined by Slovenia in 1999, Croatia in 2007 and Hungary in 2013. The vision was to pool together the donor organs and create a centralised waiting list in order to optimise HLA-matching and improve transplant outcomes. However, the early HLA-based kidney allocation system led to a high percentage of highly-sensitised, long waiting, rare HLA-phenotype and HLA-homozygous patients on the waiting list, as well as large imbalances of exchange between countries.⁵⁰

In 1996 the new Eurotransplant Kidney Allocation System (ETKAS) was introduced in order to address these issues.⁵¹ This was a points-scoring system based on HLA-mismatch, mismatch probability, waiting time, distance between donor and transplant centre, national balance of exchange, medical urgency and paediatric age. ETKAS remains in place to date.⁵² Points are awarded according to the number of HLA-mismatches (0-6), and uniquely equal weighting is given to HLA-A, -B and -DR loci. Mismatch probability is a measure of the likelihood of finding a 0 or 1 HLA-mismatched donor, based on the frequencies of HLA-antigens in the Eurotransplant donor pool. Waiting time was counted from date of registration until April 2000, and thereafter from date of first dialysis.⁵⁰ Paediatric status was previously defined as aged <16 years, but since 2010 those >16 years with growth potential proven by an X-ray of the hand are granted paediatric status. Paediatric patients are assigned additional waiting points according to the age of listing, are given double points for zero HLA-mismatched donors and since 2010 are given priority for donors < 16 years.⁵³ Since 2013, previous kidney donors are given a one off bonus of 500 extra points upon registration to the waiting list. A distinctive feature of ETKAS is the inclusion of medical urgency in the allocation score. ETKAS has been successful in transplanting a higher percentage of long waiting, highly-sensitised, rare HLA-phenotype and paediatric patients, and equalising the international imbalances in organ exchange.^{54, 55}

Eurotransplant was the first organisation to develop special allocation programs for specific groups of patients (Figure 2). The Acceptable Mismatch Program (AMP) was introduced in 1996 for highly-sensitised patients (PRA >85%), where it is determined which HLA-antigens the patient does not have antibodies against, and priority is given for any donor with acceptable antigens.^{56, 57} The Eurotransplant Senior Program (ESP) started in 1999, in which non-sensitised recipients aged >65 years are prioritised for donors >65 years irrespective of

HLA-matching. Allocation is based on medical urgency and waiting time only, and preferentially on a local basis to minimise cold ischaemia time.^{58, 59} These programs have been successful in increasing the number of transplants and shortening the waiting time for these groups of patients.⁶⁰⁻⁶³

Scandiatransplant

Scandiatransplant was formed in 1969 as a collaboration between the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). Kidneys were originally exchanged exclusively on the basis of HLA-matching, but current criteria include priority for highly-sensitised and paediatric patients.⁶⁴ Unlike most schemes, it does not employ the use of a points system. There is mandatory exchange of at least one donor kidney when a patient on the waiting list has zero HLA-mismatches, defined acceptable mismatches as part of the Scandiatransplant acceptable mismatch program (STAMP) (see below) or is a paediatric patient (<16 years at registration) with a maximum of 2 HLA-A or -B mismatches for a donor <40 years. Priority is given to highly-sensitised patients (PRA ≥ 80%), followed by those with acceptable mismatches, followed by sensitised patients (PRA 10-80%). Only blood group identical exchanges are allowed and donor-recipient age differences of over 30 years are not permitted. There is strict control of balance of exchange and kidneys are required to be paid back within 6 months. For all other kidneys that do not meet the mandatory exchange criteria, allocation is via local transplant centre policies.⁶⁵

The STAMP program was introduced in 2009. Patients may be accepted onto the program with a PRA ≥ 80% and minimum waiting time of 1 year (not necessary for paediatric patients). Within the first 3 years of the program, the number of transplanted highly-

sensitised patients increased significantly and the mean waiting time for these patients dropped from 42 to 37 months.⁶⁶

Israel

The Israeli parliament passed the Organ Transplantation Law in 2008 in order to tackle 3 major barriers to organ donation in Israel.⁶⁷ Firstly, it banned the previously legal insurance funding for overseas transplants and declared organ trafficking a criminal offence. Secondly, it clearly defined brain death in a way that was acceptable to both the medical and religious communities. Thirdly, it launched a major campaign to promote organ donation based on reciprocal altruism, by granting allocation priority to registered organ donors (3 years prior to listing), previous living donors and first-degree relatives of deceased donors. The measures have significantly reduced transplant tourism and increased both living and deceased donation and transplantation rates.⁶⁸⁻⁷⁰

The allocation system in Israel is a simple point scoring system. Points are awarded for waiting time (from date of first dialysis), age, HLA-mismatch, and level of sensitisation. Age points include priority for paediatric patients but also for younger adults over older adults. There is age-matching of donors and recipients <18 and >60 years. Points for sensitisation are awarded incrementally for each 25% increase in PRA, therefore providing some priority for patients who are moderately sensitised.⁷¹

Spain

Spain is renowned as a world leader in organ donation.^{72, 73} Although Spain's "opt-out" system legally allows presumed consent for organ donation, consent from relatives is always sought. The success of the Spanish Model is instead attributed for the most part to a network of highly trained donor coordinators.⁷⁴ Since the program was introduced in 1989 donation rates have dramatically increased from 14 to 36 donors per million population (pmp), which is almost double the average European country.⁷² Remarkably, donation rates are equal amongst native as well as immigrant populations.²

The high donation rate in Spain allows for most allocation to occur on a local basis. Criteria vary by region, but include waiting time, HLA-matching, ABO blood group, age, height, weight and primary renal diagnosis.^{74, 75} If a recipient cannot be found on local waiting lists, kidneys are offered regionally and then nationally. There is also a national exchange system for highly-sensitised recipients (PRA >80%) and an "old for old" program based solely on age-matching.⁷⁶

France

The French national kidney allocation system was first introduced in 1996. Kidneys are allocated on three priority levels: local, regional and national. National priority was given to all zero HLA-mismatched recipients until 2004, and thereafter restricted to recipients with PRA>5%.⁷⁷ Highly-sensitised patients (PRA>80%) are prioritised nationally for kidneys with a maximum of 1 HLA-mismatch, and since 2004 this also includes kidneys with "acceptable mismatches".⁷⁷ All paediatric recipients are prioritised on a national level for paediatric donors (paediatric definition increased from <16 to <18 years in 2004) and on a regional level for donors <30 years.⁷⁷ An expert kidney advisory panel can designate national priority for

emergency situations such as loss of dialysis access. If a retrieved organ does not trigger any national or regional priorities, it is allocated locally via a points scoring system introduced in 2006. This includes recipient age, waiting time, HLA-mismatch and donor-recipient age difference.⁷⁸

Discussion

Given the tremendous impact of kidney allocation policy at both an individual as well as a societal level, allocation schemes should be continually reviewed and adapted in line with the evolving medical, ethical and social landscape of kidney transplantation. This paper examined the allocation schemes of several countries in which deceased donor kidney transplantation is an accepted and well-established practice. In these jurisdictions, the creation of national transplant organisations has been fundamental to the standardisation and regulation of the organ offering process. Local centre-based allocation decisions that were largely led by HLA-matching and clinician choice have been mostly superseded by national (and sometimes international) protocols that are publicly available, enabling their evaluation. Despite differences in their specific criteria, all of these allocation policies strive for the same core principles of transparency, accountability and equity of access to kidney transplantation. The importance of this ethical framework for organ allocation is set out in guiding principles by the World Health Organisation and in The Declaration of Istanbul.^{79, 80} Allocation schemes that are designed around the preferences of all relevant stakeholders and supported by legislation are fundamental to the effective governance of organ donation and transplantation programs. It is evident that in the absence of such oversight, vulnerable populations are at risk of injustice and exploitation through unethical practices such as organ trafficking, transplant commercialism and transplant tourism.

A further step forwards in improving the objectivity of allocation has been the introduction of point-scoring systems, which can be adjusted according to changing scientific evidence, clinical practice or public expectations. Simulation plays an important role in estimating the impact of proposed changes to allocation systems. Specific outcome measures such as life years gained from transplant or the proportion of kidneys allocated to specific patient groups can be simulated with historical data to produce optimal score weights. Although limited by unpredictable human behaviour (i.e. organ acceptance decisions), simulation is becoming a valuable evidence-based tool in allocation system development.

In more ethnically diverse populations, organ sharing based largely on HLA-matching has led to marked inequity of access for ethnic minorities, necessitating more complex algorithms to address this. These inequity issues, combined with evidence for a diminishing effect of HLA-matching on graft survival in the era of improved immunosuppressive therapy,⁸¹ have prompted revisions to reduce its weighting in most, but not all policies. While some countries have eliminated allocation priority for HLA-A and/or -B matching, this has not been widely implemented, and indeed equal weighting for matching at each of the three HLA-loci is preserved in some allocation systems (Table 4). Poorly HLA-matched grafts are more likely to result in HLA-sensitisation and in the event of graft failure this jeopardises the chances of HLA-compatible re-transplantation. The level of HLA-matching and in particular HLA-DR matching are of particular importance for younger patients who are likely to require more than one graft over the course of their lifetime. Increased mismatches at first transplant are associated with a higher degree of sensitisation, longer waiting time, reduced likelihood of re-transplantation and decreased re-graft survival.⁸² Many schemes have addressed this by prioritising younger patients for well-matched grafts. For patients who are highly-sensitised,

the targeted approach of “Acceptable Mismatch Programs” adopted by many countries, have proved successful in improving access to transplantation for these patients. Waiting time has become the dominant factor of allocation in many schemes as concerns over inequity have risen. In the US, this was illustrated by a complete reversal of weighting in allocation; where previously waiting time served mostly as a tie-breaker between two similarly HLA-matched recipients, HLA-match became the deciding factor between patients with similar waiting times.⁸³

The severe shortage of donors, as well as an ageing and more infirm population, has led to increasing use of more “marginal” organs. Despite reduced graft survival, they can offer certain patients improved life expectancy when compared with staying on dialysis.^{32, 84, 85} However, in order to optimise any benefit gained, careful donor and recipient selection and matching is required. Remarkably, in some countries there are no distinct schemes for allocating marginal grafts. While Eurotransplant and Spain have instituted specific “Old for Old” programs, the UK and France have incorporated donor-recipient age matching into their allocation systems. Nevertheless, these approaches have been criticised for using chronological age as a surrogate of graft function and recipient survival, when many other important factors have been described. The previous US ECD scheme was a step forwards in classifying the quality of donor organs based on several validated donor risk factors, in addition to age. However, the scheme was criticised for the dichotomous stratification of donor kidneys as ECD or non-ECD, when in reality the risk of graft failure is better characterised by a continuous scale.⁴¹ The new US system reflects this with the KDPI.⁸⁶ This continuous measure of predicted graft survival is used to allocate kidneys based on a recipient’s estimated post-transplant survival. Although this applies only to the 20% of recipients with the longest estimated survival, this degree of survival matching is a first in

kidney allocation. In New Zealand, a similar prognostic index of post-transplant survival based on multiple patient risk factors is utilised in a novel way to provide an objective criterion (5-year survival >80%) for access to the waiting list. This evidence-based risk stratification ensures those listed have a reasonable expectation of receiving and surviving a transplant. A nationally applicable survival probability threshold for listing, is perhaps the most equitable way of determining access to the waiting list, whilst also ensuring optimal use of a scarce resource.

The transplant community should be proud of the significant progress that has been achieved in improving the transparency, accountability and equity of kidney allocation. However, in the context of the continuing shortage of donor organs, further work is needed to reduce the discard of donated kidneys and to optimise the efficiency of allocation.

Conclusion

Despite striking shifts in the demographics of donor and recipient populations, there has been relatively little change in deceased donor kidney allocation over the past decade. Given that the donor shortage shows no signs of abatement, it may be timely to consider a radical change in the ideology governing kidney allocation towards “the right kidney to the right recipient”. Sophisticated donor-recipient survival matching may well be the optimal compromise between utility and equity that the transplant community strives for.

Tables and Figures

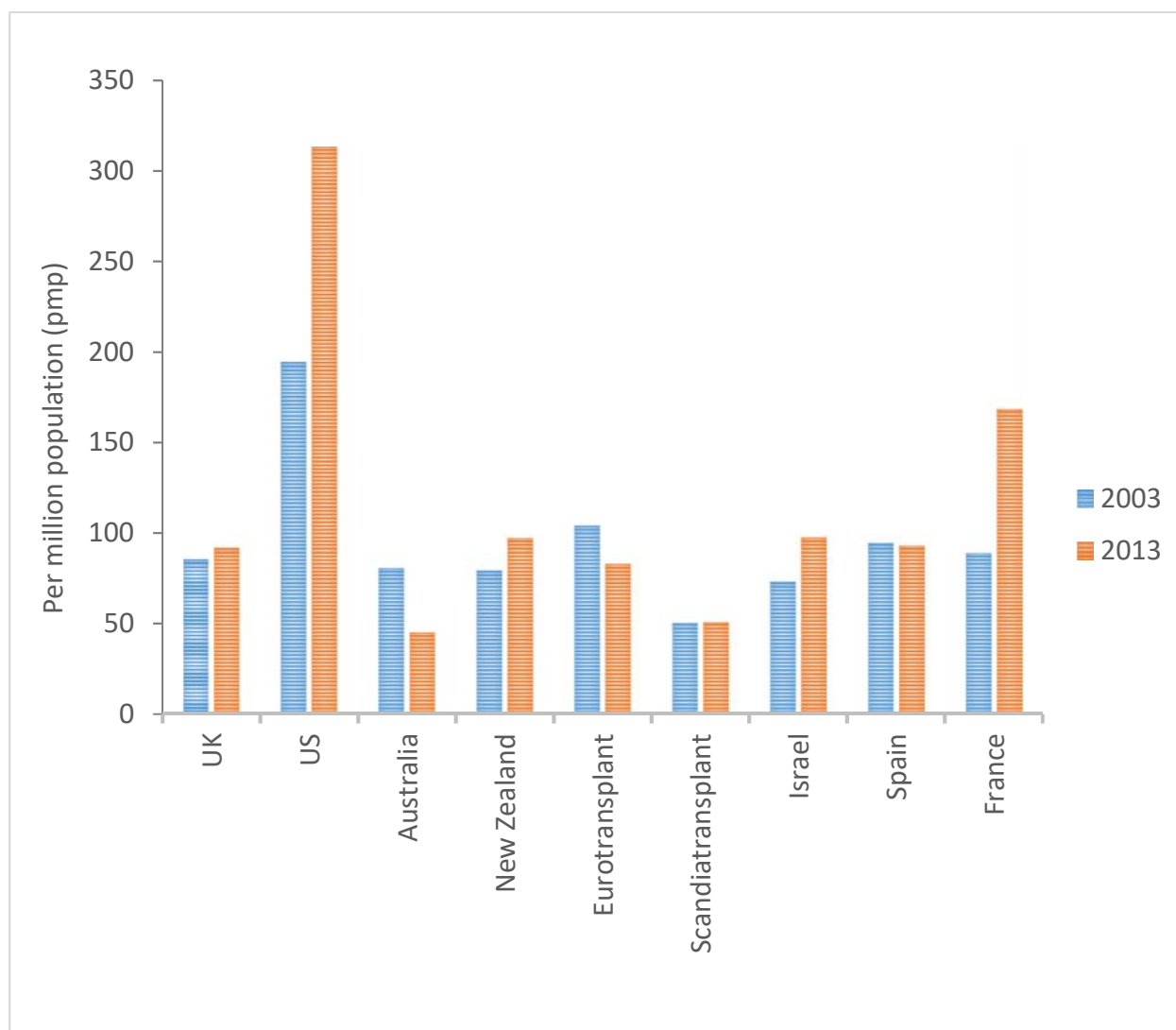


Figure 1. Patients on Kidney Transplant Waiting List 2003 vs 2013

Eurotransplant 2003 = Austria, Belgium, Germany, the Netherlands, Luxembourg and Slovenia.

Eurotransplant 2013 = Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Luxembourg and Slovenia

Scandiarttransplant = Denmark, Finland, Iceland, Norway and Sweden

Data sources: UK,⁸⁷⁻⁸⁹ US,^{3, 90, 91} Australia,^{92, 93} New Zealand,^{92, 93} Eurotransplant,^{94, 95} Scandiarttransplant,^{96, 97} Israel,^{98, 99} Spain,^{98, 99} France⁹⁸⁻¹⁰⁰

	UK		US		Australia		New Zealand		Eurotransplant ^a		Scandiatransplant ^b		Israel		Spain		France	
Year	2003	2013	2003	2013	2003	2013	2003	2013	2003	2013	2003	2013	2003	2013	2003	2013	2003	2013
Population (million) ^c	59.5	64.0	291.0	317.1	19.7	23.3	4.0	4.5	118.8	133.8	24.4	26.1	6.4	7.8	42.5	46.5	60.5	63.8
Total kidney transplants																		
n	1836	3256	15138	16895	543	882	111	115	3991	4586	926	1103	126	264	2051	2552	2127	3074
pmp	30.9	50.9	52	53.3	27.6	37.9	27.8	25.6	33.6	34.3	38	42.3	19.7	33.8	48.3	54.9	35.2	48.2
DD transplants																		
n	1386	2142	8668	11163	325	630	67	57	3345	3183	654	756	55	128	1991	2170	1991	2673
pmp	23.3	33.5	29.8	35.2	16.5	27	16.8	12.7	28.1	23.8	26.8	29	8.6	16.4	46.8	46.7	32.9	41.9
LD transplants																		
n	450	1114	6470	5732	218	252	44	58	646	1403	272	347	71	136	60	382	136	401
pmp	7.6	17.4	22.2	18.1	11.2	10.8	11	12.9	5.4	10.5	11.1	13.3	11.1	17.4	1.4	8.2	2.2	6.3
Patients on waiting list at year end																		
n	5074	5881 ^d	56514	99253	1591	1056	318	438	12382	11120	1231	1333	469	762	4026	4328	5380	10736
pmp	85.3	91.9	194.2	313	80.8	45.3	79.5	97.3	104.2	83.1	50.5	51.1	73.3	97.7	94.7	93.1	88.9	168.3
Died on waiting list																		
n	298	279	3895	4644	45	3	x	x	646	593	20	74	16	30	x	x	113	252
pmp	5	4.4	13.4	14.6	2.3	0.1	x	x	5.4	4.4	0.8	2.8	2.5	3.8	x	x	1.9	3.9
Median waiting time years																		
	2.3	2.7	3.2	4.5	3.7	2.7	x	x	3.3	3.7	1.1	1.2	x	x	x	x	1.4	2.4

Table 1. Kidney Transplant and Waiting List Figures 2003 vs 2013

(PMP; per million population, DD; Deceased donor, LD; Living donor)

x Data not available

^a Eurotransplant 2003 = Austria, Belgium, Germany, the Netherlands, Luxembourg and Slovenia. Eurotransplant 2013 = Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Luxembourg and Slovenia

^b Scandiatransplant = Denmark, Finland, Iceland, Norway and Sweden

^c Data from United Nations Population Division

^d Note this number represents a downward trend since 2009

Data sources: UK,⁸⁷⁻⁸⁹ US,^{3, 90, 91} Australia,^{92, 93} New Zealand,^{92, 93} Eurotransplant,^{94, 95} Scandiatransplant,^{96, 97} Israel,^{98, 99} Spain,^{98, 99} France⁹⁸⁻¹⁰⁰

	Actual DBD Kidney only transplants in the UK			
	1 Jan 03 - 31 Dec 03		1 Jan 13 - 31 Dec 13	
	n	%	n	%
Number of transplants	1133		1161	
HLA-mismatches				
Level 1 (000 MM)	193	17.0	216	18.6
Level 2 (0DR+0/1B MM)	588	51.9	437	37.6
Level 3 (0DR+2B or 1DR+0/1B MM)	270	23.8	477	41.1
Level 4 (2B+1DR or 2DR MM)	82	7.2	31	2.7
Matchability				
Easy (1-3)	538	47.5	441	38.0
Moderate (4-7)	429	37.9	512	44.1
Difficult (8-10)	165	14.6	207	17.8
Highly-sensitised (cRF>85%)	53	4.7	195	16.8
Waiting time				
<1 yr	497	43.9	236	20.3
1-3 yrs	392	34.6	370	31.9
3-5 yrs	143	12.6	326	28.1
5-7 yrs	48	4.2	159	13.7
>=7 yrs	53	4.7	70	6.0
Recipient age				
0-5	10	0.9	7	0.6
6-11	21	1.9	17	1.5
12-17	52	4.6	34	2.9
18-29	122	10.8	107	9.2
30-39	200	17.7	171	14.7
40-49	273	24.1	278	23.9
50-59	266	23.5	269	23.2
60-69	163	14.4	209	18
>=70	26	2.3	69	5.9
Donor-recipient age difference				
<15 yrs	688	60.7	732	63.0
15-25 yrs	260	22.9	299	25.8
>25 yrs	185	16.3	130	11.2
Recipient blood group				
O	467	41.2	512	44.1
A	460	40.6	423	36.4
B	150	13.2	166	14.3
AB	56	4.9	60	5.2
Homozygosity				
HLA-A	161	14.2	148	12.7
HLA-B	90	7.9	84	7.2
HLA-DR	103	9.1	146	12.6
HLA-A,B,DR	16	1.4	29	2.5
Graft number				
1	954	84.2	939	80.9
2	149	13.2	186	16.0
3	24	2.1	31	2.7
4	6	0.5	5	0.4
Diabetic	74	6.5	75	6.5
Gender (Male)	697	61.5	717	61.8
Ethnicity				

White	981	86.6	824	71.0
Asian	96	8.5	205	17.7
Black	43	3.8	95	8.2
Other	11	1.0	31	2.7
Not Reported	2	0.2	6	0.5
Exchange				
Local centre	402	35.5	189	16.3
Local area	399	35.2	604	52.0
Other	332	29.3	368	31.7
Median CIT	18.5 hrs	(IQR 15.9 - 22.4)	14.5 hrs	(IQR 11.4 - 17.9)
1-year Graft Survival	91.2%	(95% CI 89.3 – 92.7)	94.1%	(95% CI 92.4 – 95.4)
1-year Patient Survival	95.5%	(95% CI 93.9 – 96.7)	95.9%	(95% CI 94.2 – 97.1)

Table 2. Transplant characteristics for DBD kidney only transplants in the UK 2003 vs 2013.

(DBD; Donor after Brain Death, HLA; Human Leukocyte Antigen, MM; Mismatch, cRF; Calculated Reaction Frequency, CIT; Cold Ischaemia Time)

Data source: NHSBT Data Request. Based on data as of January 20, 2015.

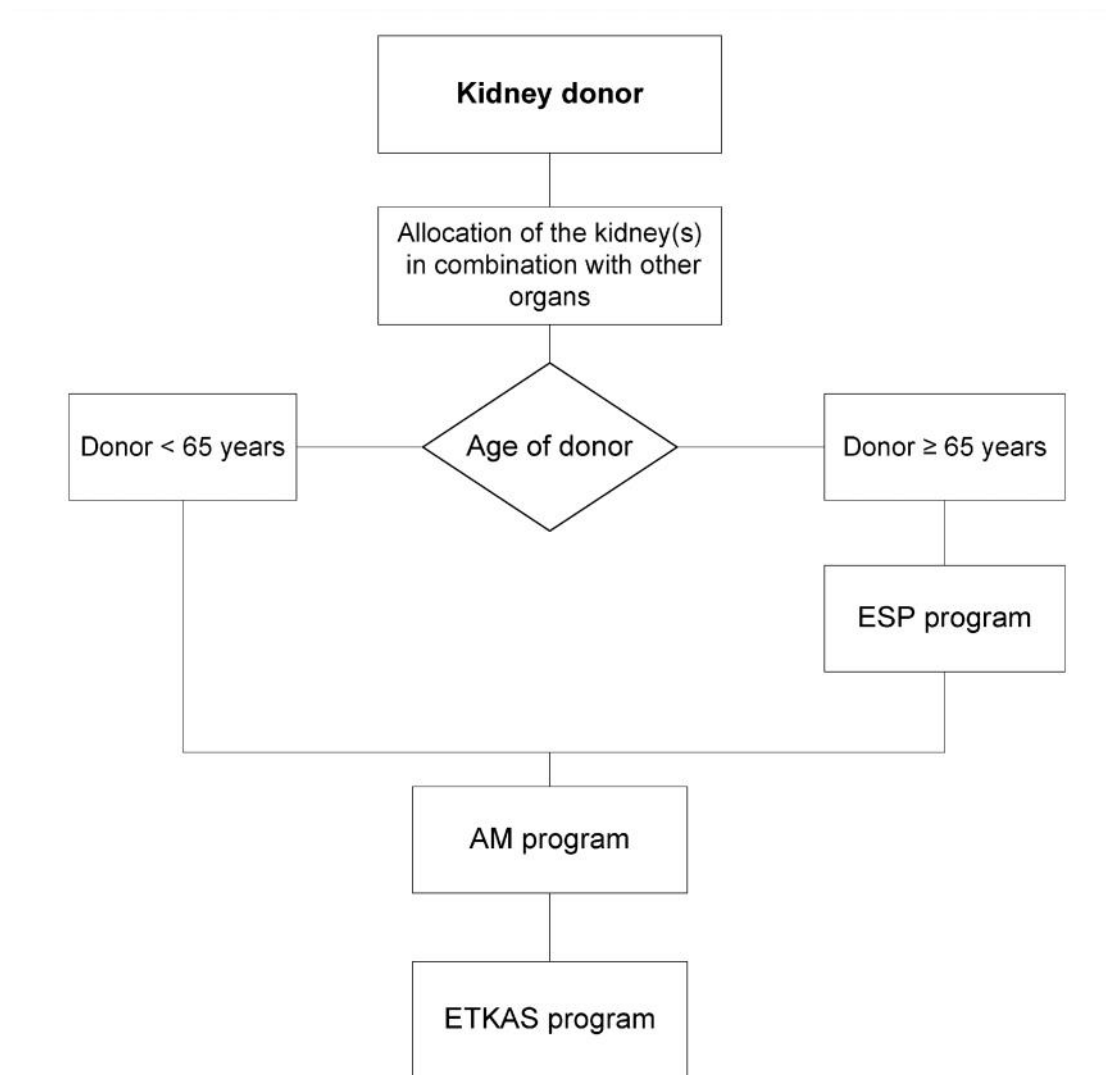


Figure 2. Eurotransplant kidney allocation flow chart

(ESP; Eurotransplant Senior Program, AM; Acceptable Mismatch, ETKAS; Eurotransplant Kidney Allocation System)

Source: Eurotransplant Manual Version 4.1a.⁵²

Donor characteristic

Age
Height
Weight
Ethnicity
History of hypertension
History of diabetes
Cause of death
Serum creatinine
Hepatitis C Virus status
Donation after circulatory death status

Table 3. Factors used to calculate the Kidney Donor Risk Index (KDRI)

Source: Organ Procurement and Transplantation Network Policy 8.²⁸

	UK		US			Australia		New Zealand	
	2003	2013	2003	2013	2014	2003	2013	2003	2013
<i>HLA-mismatch</i>									
<i>DR</i>	+	+	+	+	+	+	+	+	+
<i>B</i>	+	+	+	-	-	+	+	+	+
<i>A</i>	+	-	-	-	-	+	+	+	+
<i>HLA loci importance</i>	DR > B / A	DR > B	DR > B	DR only	DR only	DR > B / A	DR > B / A	DR > B > A	DR > B > A
<i>Waiting time</i>	+	+	+	+	+	+	+	+	+
<i>Waiting time definition</i>	Listing date	Listing date	Listing date	Listing date	Start of dialysis	Start of dialysis	Start of dialysis	Latest of start of dialysis or listing date	Latest of start of dialysis or listing date
<i>Priority for paediatric recipients</i>	+	+	+	+	+	+	+	+	+
<i>Definition of paediatric recipient</i>	<18 years	<18 years	<18 years	<18 years	<18 years	<18 years	<18 years, first dialysis <17 years and on dialysis for >1 year	<15 years	<15 years
<i>Recipient age</i>	+	+ ^b	-	-	+	-	-	-	-
<i>Donor-recipient age matching</i>	+	+	-	-	-	-	-	+	-
<i>Priority for highly-sensitised recipients</i>	+	+	+	+	+	+	+	-	-
<i>Applicable level of PRA/cPRA (%)</i>	85	85	80	80	20-100 ^c	50	50/80 ^d	N/A	N/A
<i>Priority for HLA homozygous recipients</i>	DR	DR, B	-	-	-	-	-	-	-
<i>Local allocation priority</i>	+	+	+	+	+	+	+	-	-
<i>Balance of exchange</i>	+	-	+	+	-	+	+	-	-
<i>Point scoring systems in use</i>	+	+	+	+	+	+	+	+	+
<i>Special program for allocation of marginal donors</i>	-	-	+	+	+	-	-	-	-
<i>Other allocation criteria / features</i>	Matchability score	Defaulting of rare HLA antigens	Priority for prior organ donors	Priority for prior organ donors	Priority for prior organ donors, EPTS, KDPI	Min 30% locally allocated kidneys on waiting time alone	Min 30% locally allocated kidneys on waiting time alone		EPTS >80% defines eligibility for waiting list, All ECD biopsied and scored by Remuzzi classification

	<i>Eurotransplant</i>		<i>Scandiatransplant</i>		<i>Israel</i>		<i>Spain ^a</i>		<i>France</i>	
	2003	2013	2003	2013	2003	2013	2003	2013	2003	2013
<i>HLA-mismatch</i>										
<i>DR</i>	+	+	+	+	+	+			+	+
<i>B</i>	+	+	+	+	+	+			+	+
<i>A</i>	+	+	+	+	+	+			+	+
<i>HLA loci importance</i>	DR = B = A	DR = B = A	DR > B / A	DR > B / A	DR > B / A	DR > B / A	?	?	DR = A = B	DR > A / B
<i>Waiting time</i>	+	+	-	-	+	+	+	+	+	+
<i>Waiting time definition</i>	Start of dialysis	Start of dialysis	N/A	N/A	Start of dialysis	Start of dialysis	?	?	?	?
<i>Priority for paediatric recipients</i>	+	+	+	+	+	+	+	+	+	+
<i>Definition of paediatric recipient</i>	<16 years	<16 years or >16 years and growth potential proven by Xray of hand	<16 years at registration	<16 years at registration	<18 years	<18 years	?	?	<16 years	<18 years
<i>Recipient age</i>	-	-	-	-	+	+	+	+	-	+
<i>Donor-recipient age matching</i>	-	-	+	+	+	+	+	+	-	+
<i>Priority for highly-sensitised recipients</i>	+	+	+	+	+	+	+	+	+	+
<i>Applicable level of PRA/cPRA (%)</i>	85	85	80	80	26-100 ^c	26-100 ^c	80	80	80	85
<i>Priority for HLA homozygous recipients</i>	+	+	-	-	-	-	-	-	-	-
<i>Local allocation priority</i>	+	+	-	-	-	-	+	+	-	+
<i>Balance of exchange</i>	+	+	+	+	-	-	-	-	-	-
<i>Point scoring systems in use</i>	+	+	-	-	+	+	-	-	-	+
<i>Special program for allocation of marginal donors</i>	+	+	-	-	-	-	-	-	-	-
<i>Other allocation criteria / features</i>	Medical urgency, Mismatch probability, AMP, ESP	Medical urgency, Mismatch probability, AMP, ESP, Prior kidney donors		STAMP		Priority for registered organ donors of at least 3 yrs prior to listing	Height, Weight, PRD	Height, Weight, PRD, Old for Old		AMP

Table 4. Criteria for deceased donor kidney allocation 2003 vs 2013.

(HLA; Human Leukocyte Antigen, MM; Mismatch, PRA; Panel Reactive Antibody, cPRA; Calculated Panel Reactive Antibody, EPTS; Estimated Post-Transplant Survival Score, KDPI; Kidney Donor Profile Index, AMP; Acceptable Mismatch Program, ESP; Eurotransplant Senior Program, STAMP; Scandiatransplant Acceptable Mismatch Program, PRD; Primary Renal Diagnosis)

^a No national allocation system. Criteria applicable only at local level

^b Age & HLA-MM combined

^c Sliding scale of points

^d >50% for 000 MM, >80% for all other MM levels

Search strategy and selection criteria

References for this review were identified by searches of PubMed and Google Scholar using the terms “kidney”, “deceased donor kidney”, “cadaver kidney” or “kidney transplant” combined with “allocation”, “offering scheme”, “distribution” or “selection criteria” for publications in any language before 30/04/2016. Data were also obtained by direct contact with national transplant registries, their websites and reports; including UK Transplant (<http://www.odt.nhs.uk/uk-transplant-registry/>), US United Network for Organ Sharing (<https://www.unos.org/>), Australia and New Zealand Dialysis and Transplant Registry (<http://www.anzdata.org.au/v1/>), Eurotransplant (<https://www.eurotransplant.org/cms/>), Scandiatransplant (<http://www.scandiatransplant.org/>), Israel (<https://www.adi.gov.il/>), Spain Organizacion nacional de trasplantes (<http://www.ont.es/>) and France agence de la biomedicine (<http://www.agence-biomedecine.fr/>).

Contributors

All authors contributed to the design of the review. DW conducted the literature review and submitted data requests, DW and GCO drafted the manuscript, DW, GCO, CW, JAB, JLF and RJ revised the drafts and approved the final version.

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